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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,094	08/26/2005	Norbert Lange	BHJ7USA	9375

270 7590 02/27/2008

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
02/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,094	LANGE ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-24,30-34 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-24,30-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Invention 2 in the reply filed on 2/5/08 is acknowledged.

Claims 1, 25-29, 35, and 36 were canceled. Claims 2-24 were amended to join the elected group.

Claims 2-24, 30-34, and 37 remain pending and are under consideration.

Specification/Drawings

Figure 2 refers to structures 12a and 12b, and Figure 5 refers to structure 20, however these structures do not appear to be defined in the specification. Accordingly the Figures and specification are objected to.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-24, 30-34, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-24, 30-34, and 37 are indefinite because they recite "the internalization" without antecedent basis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-10, 30-34, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Magda et al (US 5,567,687).

Magda taught compounds comprising an oligonucleotide conjugated to a texaphyrin fluorophore (texaphyrins are porphyrins). The complexes could be used to cleave target DNA to which the oligonucleotide was complementary. The oligonucleotide could also function as a site-directing molecule that provides localization to tumors, wherein tumors are subsequently treated by photodynamic therapy via illumination of the texaphyrin and subsequent generation of cytotoxic radicals like singlet oxygen. See abstract; column 3, lines 12-20 and 44-60; column 4, lines 23-31; and column 11, lines 14-17; and 22-38. Texaphyrins are excited by light in the range of 700-900 nm, and Magda exemplifies the use of laser light at 732 nm and 150 J/cm2 for photodynamic therapy. Light was administered 1 hour after administration of the texaphyrin. See column 3, lines 44-51; column 8, lines 38-64; and column 36, lines 24-43).

Magda also taught a compound comprising an oligonucleotide capable of forming a hairpin and comprising a texaphyrin and a quencher, wherein the texaphyrin and quencher are brought into proximity when the oligonucleotide is in hairpin conformation,

but are separated in the presence of a target sequence allowing activation of the texaphyrin. In one embodiment, the quencher is another texaphyrin. See Fig. 9A; Fig. 10A; and column 39, line 39 to column 40, line 14. Magda suggested use of the quenchable hairpin compound as a probe, but did not explicitly suggest its use in killing cells.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the quenchable hairpin compound of Magda to kill cells. The compound has all of the structural and functional characteristics of the other oligonucleotide conjugates of Magda that are specifically intended to target and kill tumors. Thus, at a minimum, it is an art-recognized equivalent which would be obvious to use in such methods (see MPEP 2144.06). The hairpin compound has the additional advantage of a quenching agent that will allow excitation of the texaphyrin only in the presence of target nucleic acids, thereby mitigating non-specific effects.

Thus the invention as a whole was prima facie obvious.

Claims 11-19, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Magda et al (US 5,567,687) as applied to claims 72-10, 30-34, and 37 above, and further in view of Berg et al (US 6,680,301).

The teachings of Magda are discussed above and render obvious a method of killing cells by incubating them with a compound comprising a hairpin oligonucleotide conjugated to a fluorophore and a quencher, wherein excitation of the fluorophore leads to the production of singlet oxygen, and such excitation occurs when the fluorophore is

illuminated with excitatory light and the oligonucleotide is bound to a target nucleic acid such that the quencher cannot quench the fluorophore.

Magda did not teach a complex between the compound and a polycationic carrier that increases internalization of the compound.

Berg taught methods of photochemical internalization of complexes comprising photosensitizers and nucleic acids. It is apparent from the teachings of Berg that the use of polylysines and antibodies to induce internalization of nucleic acids into cells was well known prior to the time the instant invention was filed, and that complexes or conjugates comprising photosensitizers, nucleic acids, and carriers such as antibodies and/or polylysine could be internalized by cells. See e.g. column 2, lines 61-64; column 6, lines 44-56; and column 7, lines 31-37. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Magda by inclusion of a carrier molecule intended to facilitate cellular uptake, as taught by Berg.

Regarding claim 11, the complex comprising polylysine and the compound of Magda is considered to be a bimolecular compound.

Regarding claim 16, the use of ionic or covalent attachment of the oligonucleotide to the carrier is considered to be a matter of design choice.

Claims 11-17, 19, 20, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Magda et al (US 5,567,687) as applied to claims 72-10, 30-34, and 37 above, and further in view of Beug et al (US 5,354,844).

The teachings of Magda are discussed above and render obvious a method of killing cells by incubating them with a compound comprising a hairpin oligonucleotide conjugated to a fluorophore and a quencher, wherein excitation of the fluorophore leads to the production of singlet oxygen, and such excitation occurs when the fluorophore is illuminated with excitatory light and the oligonucleotide is bound to a target nucleic acid such that the quencher cannot quench the fluorophore.

Magda did not teach a complex between the compound and a polycationic carrier that increases internalization of the compound.

Beug taught polycationic carriers for transporting nucleic acids such as oligonucleotides into cells. The carriers comprised a polycation such as polylysine or histone conjugated to transferrin. The polycation moiety of the conjugate formed an electrostatic complex with the oligonucleotide, and the transferrin moiety facilitated receptor-mediated endocytosis via the transferrin receptor. See abstract, column 5, lines 31-43; and column 6, lines 42-47.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Magda by inclusion of a carrier molecule intended to facilitate cellular uptake, such as the one taught by Beug. One would have been motivated to do so in order to improve the ability of the oligonucleotide of Magda to penetrate cells, and to protect the oligonucleotide from nucleases. Thus the invention as a whole was prima facie obvious.

Regarding claim 11, the complex comprising polylysine and the compound of Magda is considered to be a bimolecular compound.

Regarding claim 16, the use of ionic or covalent attachment of the oligonucleotide to the carrier is considered to be a matter of design choice.

Claims 12-14 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Magda et al (US 5,567,687) as applied to claims 2-10, 30-34, and 37 above, and further in view of Wasan (US 5,965,542).

The teachings of Magda are discussed above and render obvious a method of killing cells by incubating them with a compound comprising a hairpin oligonucleotide conjugated to a fluorophore and a quencher, wherein excitation of the fluorophore leads to the production of singlet oxygen, and such excitation occurs when the fluorophore is illuminated with excitatory light and the oligonucleotide is bound to a target nucleic acid such that the quencher cannot quench the fluorophore.

Magda did not teach a complex between the compound and a liposomal carrier that increases internalization of the compound.

Wasan taught polycationic liposomal vesicles for transferring oligonucleotides into cells. The liposomes contained cationic lipids and neutral lipids such as diacylphosphatidylcholine and cholesterol (see column 5, lines 56-61), and were 100-150 nm in diameter. See abstract; column 6, lines 31-35 and 57-60; column 7, lines 22-31 and 38-45; and column 10, lines 41-44.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Magda by inclusion of a liposomal carrier intended to facilitate cellular uptake, such as the one taught by Wasan. One would have been

motivated to do so in order to improve the ability of the oligonucleotide of Magda to penetrate cells, and to protect the oligonucleotide from nucleases. Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Richard Schnizer, Ph.D.
Primary Examiner

Art Unit 1635